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Title:

Process

Technical field of the invention:

The present invention relates to a process for the preparation of iohexol, 5-[N- (2,3-dihydroxypropyl) -acetamido]-N,N'-bis(2,3 -dihydroxypropyl)-2,4,6-triiodoisophtalamide, and to a method of purifying iohexol.

Description of related prior art:

Iohexol is a non-ionic iodinated X-ray contrast agent with the trade name OMNIPAQUE® and is one of the most used products in diagnostic X-ray procedures.

The manufacture of iohexol involves a multistep chemical synthesis. The present invention is directed to the last step of this synthesis i.e. the synthesis of iohexol from 5-(acetamido)-N,N'-bis(2,3-dihydroxypropyl)-2,4,6 triiodoisophtalamide (hereinafter "5-Acetamide") and to the purification of the crude iohexol from this step.

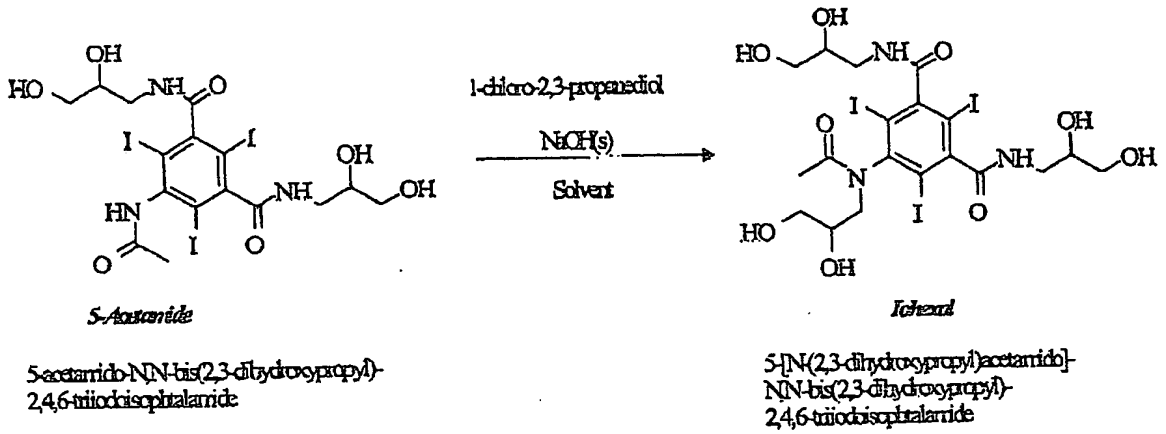
The manufacture of iohexol is disclosed for example in US-4,250,113. In the last step of the multistep chemical synthesis presented here crude iohexol is produced from 5-Acetamide and the solvent used is propylene glycol. The solvent is then evaporated from the crude iohexol and then iohexol is recrystallised twice from butanol.

WO-A-02/083623 discloses the purification of crude iohexol using 1-methoxy-2-propanol as the solvent optionally in a mixture with other solvents.

WO-A-98/08804 discloses the use of 2-methoxy-ethanol and optionally isopropanol both in the alkylation step of 5-Acetamide and in the purification of crude iohexol.

It is still a need to select a solvent that further improve the overall process in both the alkylation step and in the purification of iohexol in terms of further increasing the purity of final purified iohexol.

In the last step in the chemical synthesis of iohexol, which is referred to as the alkylation step, 5-Acetamide in solution is reacted with an alkylation agent such as e.g. 1-chloro-2,3-propandiol to introduce the 2,3-dihydroxypropyl group at the nitrogen of the 5-acetamido group:



5-acetamido-N,N-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophtalamide

5-[N-(2,3-dihydroxypropyl)acetamido]-N,N-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophtalamide

Scheme 1.

O-alkylated by-products are also formed in the alkylation step when the alkylation occurs at one of the oxygen atoms at one of the hydroxy groups. One important aspect of the invention is to limit the concentration of these O-alkylated by-products in the final purified iohexol. Another important aspect of the invention is to limit the concentration of unidentified by-products, referred to as other impurities, in the final purified iohexol. In addition the solvents used should be easily available. The present invention improves the process for preparation of iohexol meeting the above needs.

Summary of the invention:

It has now surprisingly been found that the use of a C_1-C_5-monoalkylether of a C_3-C_{10} alkylene-glycol as solvent in the alkylation of 5-Acetamide will give crude iohexol in almost quantitative yield. After the alkylation step the salt content is optionally reduced before the purification step. Before the purification step most of the solvent from the alkylation step is distilled off, to produce a concentrated solution from which iohexol is further separated. The following purification step is performed in the same C_1-C_5-monoalkylether of a C_3-C_{10} alkylene-glycol as used in the alkylation step. Using the invention will provide iohexol in good yield and of improved purity. As a result a minimum of purification steps will be needed.

Detailed description of the invention:

In a first embodiment the invention discloses a process for the preparation of purified iohexol comprising:

i) alkylation of 5-Acetamide with a 2,3 dihydroxypropylation agent in the presence of a base and of a solvent comprising a C_1-C_5-monoalkylether of a C_3-C_{10} alkylene-glycol, and

ii) purification of iohexol as prepared in i) comprising using the same C_1-C_5-monoalkylether of a C_3-C_{10} alkylene-glycol as used in i).

In a second embodiment the invention provides a process for the preparation of iohexol comprising reacting 5-Acetamide with a 2,3-dihydroxypropylating agent in the presence of a base and of a solvent comprising a C_1-C_5-monoalkylether of a C_3-C_{10} alkylene-glycol. This process is illustrated in scheme 1 when the solvent is a C_1-C_5-monoalkylether of a C_3-C_{10} alkylene-glycol.

The solvent in the process according to the invention comprises a C_1-C_5-monoalkylether of a C_3-C_{10} alkylene-glycol. In a preferred aspect of the invention the C_1-C_5-monoalkylether of a C_3-C_{10} alkylene-glycol is mixed with other solvents thus forming a solvent mixture. The preferred C_1-C_5-monoalkylether of a C_3-C_{10} alkylene-glycol is 1-methoxy-2-propanol. In a more preferred aspect of the invention 40–90 volume % of 1-methoxy-2-propanol is mixed with other solvents. In a most preferred aspect a solvent mixture of 1-methoxy-2-propanol and up to 40-volume % methanol is used, with 30-volume % methanol being most preferred. In a particularly preferred aspect a solvent mixture of 1-methoxy-2-propanol and up to 20-volume % water is used, with 10-volume % water being most preferred.

The solvents used in the process according to the invention are preferably used in a concentration of 0.5-2.0 ml per gram of 5-Acetamide with 0.9-1.0 ml being the most preferred concentration.

The 2,3-dihydroxypropylating agent according to the process of the invention is any 2,3-dihydroxypropanol with a leaving group attached in the 1-position. 1-halo-2,3-propandiol are preferred with 1-chloro-2,3-propandiol being the most preferred 2,3-dihydroxypropylating agent. Alternatively, glycidol may be used as the 2,3-dihydroxypropylation agent. The 2,3-dihydroxypropylation agent is preferably used in concentrations of 1.2-1.4 moles per mole of 5-Acetamide.

The alkylation step takes place in the presence of a base. The base in the process according to the invention is soluble in the reaction solvent. Alkali metal hydroxide is the preferred base and sodium hydroxide being most preferred. The base is preferably used in concentrations of 1.2-1.4 moles per mole of 5-Acetamide.

The alkylation step according to the invention is preferably effected at a temperature, such as 15-50°C, with 23-25°C being the most preferred process temperature.

The alkylation step of the process according to the invention will be allowed to proceed for several hours with a preferred reaction time of 12 to 48 hours and particularly preferred from 18 to 30 hours before quenching. Quenching with an acid may be used to terminate the reaction. Inorganic or organic acids may be used and inorganic acids such as HCl are preferred.

After quenching the salt produced in the alkylation step is optionally reduced before the purification is started. The optionally reduction of the salt content is done without the need of removal of the solvents from the alkylation step.

Most of the solvents are preferably distilled off, optionally after reduction of the salt content. This is done before the purification is started thus allowing the solution of crude iohexol to be concentrated.

Before the purification is started, i.e. after the alkylation step and after the optionally step of salt content reduction, the concentration of the solvent or solvent mixtures is optionally adjusted to optimise the content of solvent with regard to the purification. In a preferred aspect a C_1-C_5-monoalkylether of a C_3-C_{10} alkylene-glycol is used to adjust the solvent content. Preferably 1-methoxy-2-propanol is used, however a solvent mixture such as a mixture of a C_1-C_5-monoalkylether of a C_3-C_{10} alkylene-glycol with methanol may be used. In a most preferred aspect the solvent amounts are adjusted to 2-6 ml 1-methoxy-2-propanol/g iohexol, 0-1 ml methanol/g iohexol and the water content is reduced to 0.001-0.3 ml water/g iohexol.

Isopropanol is optionally added at a later stage during the purification to further improve the yield.

In a preferred aspect of the purification iohexol is separated out as crystals.

The purification of iohexol according to the invention is preferably effected at a temperature range 50-130°C, dependent on pressure with a temperature range of 60-120° being most preferred.

The purification of iohexol according to the invention is preferably effected at a pressure between 0.2-2.5 bar with a pressure between 0.3 to 0.7 bar being most preferred.

The purification of iohexol according to the invention is preferably effected over a time of approximately 4 hours to 2 days. Water is optionally removed by azeotropic distillation with a C_1-C_5-monoalkylether of a C_3-C_{10} alkylene-glycol and most preferably 1-methoxy-2-propanol from the solution at any time during the purification.

The invention will hereinafter be illustrated by the non-limiting examples. All percent are in HPLC area % when not stated otherwise.

Examples:

Example 1: Synthesis of iohexol in 1-methoxy-2-propanol/methanol

1-methoxy-2-propanol (44 ml), methanol (19 ml) and sodium hydroxide (4.87 g) was added to a jacketed glass reactor and stirred for about 15 minutes at 25°C. 5-Acetamide (70 g) was added to the reactor, and the mixture stirred overnight at 45°C, before it was allowed to cool to 25°C. 1-chloro-2,3-propanediol (12.43 g) was added to the solution. After 1.5 hours, more 1-chloro-2,3-propanediol (0.83 g) was added, and the reaction was allowed to proceed for 24 hours. HPLC analysis (water/acetonitrile) of the reaction mixture gave the following results:

Iohexol	98.1 %
5-Acetamide	1.17 %
O-alkylated substances	0.58 %
Other impurities	0.1 %

Example 2: Synthesis of iohexol in 1-methoxy-2-propanol/water

1-methoxy-2-propanol (63 ml), water (7 ml) and sodium hydroxide (4.50 g) was added to a jacketed glass reactor and stirred for about 15 minutes at 25°C. 5-Acetamide (70 g) was added to the reactor, and the mixture stirred overnight at 45°C, before it was allowed to cool to 35°C. 1-chloro-2,3-propanediol (11.39 g) was added to the solution. After 3 hours, more 1-chloro-2,3-propanediol (0.83 g) was added, and the reaction was allowed to proceed for 24 hours. HPLC analysis (water/acetonitrile) of the reaction mixture gave the following results:

Iohexol	98.3 %
5-Acetamide	0.68 %
O-alkylated substances	0.81 %
Other impurities	0.3 %

Example 3: Alkylation and crystallisation in solutions containing 1-methoxy-2-propanol

1-methoxy-2-propanol (63 L), methanol (27 L) and sodium hydroxide (6.96 kg) was added to a 500 L reactor and stirred until all solids were dissolved and the temperature was below 30°C. 5-Acetamide (100 kg) was added to the reactor, and the mixture stirred overnight at 45°C before it was allowed to cool to 25°C. 1-chloro-2,3-propanediol (16.76 kg) was added to the clear solution. After 1.5 hours, more 1-chloro-2,3-propanediol (1.18 kg) was added, and the reaction was allowed to proceed for 30 hours. HPLC analysis (water/acetonitrile) of the reaction mixture gave the following results:

Iohexol	97.9 %
5-Acetamide	0.9 %
O-alkylated substances	0.83 %
Other impurities	0.4 %

The reaction was stopped by addition of hydrochloric acid (650 ml), and the reaction mixture diluted with a mixture of 1-methoxy-2-propanol (53 L) and methanol (13 L). The mixture was filtered, and the salts on the filter washed with methanol (3x10 L). The combined filtrate and wash was diluted with water (22 L) and treated with cationic ion exchange resin (AMB 200C, 80 L) and anionic ion exchange resin (IRA 67, 80 L) to a salt content of 0.006 w/w %. The solution was filtered, and the ion exchange resins washed in several stages with a mixture of water (160 L) and methanol (85 L). The combined filtrate and wash was concentrated under reduced pressure to a volume of 155 L. One half of this was taken further to crystallisation as described below.

Water was removed from the solution by azeotropic distillation. The volume was held at a constant level by replacing the distillate by 1-methoxy-2-propanol (80 L). At water content of 0.16 L/kg iohexol, further 1-methoxy-2-propanol (159 L) was added, and the solution seeded with iohexol crystals (0.26 kg). After stirring at reflux overnight, the volume of the solution was reduced by 42 L by distillation under reduced pressure (300-600 mbar). The temperature was set to 90°C, which was held for 3 hours before cooling to 60°C over 3 hours. The crystallisation mixture was stirred overnight at 60°C, filtered and washed with isopropanol (90 L, 6 portions). The yield was 48.4 kg (as dry powder), corresponding to 88-weight % corrected for

seeding material and samples. HPLC analysis (water/acetonitrile) of the crystals gave the following results:

Iohexol	99.3 %
5-Acetamide	0.15 %
O-alkylated substances	0.45 %
Other impurities	0.11 %

Claims:

1. A method for the purification of iohexol comprising:

i) alkylation of 5-(acetamido)-N,N'-bis(2,3-dihydroxypropyl)-2,4,6,triiodoisophtalamide with a 2,3 dihydroxypropylation agent in the presence of a base and of a solvent comprising a C_1-C_5-monoalkylether of a C_3-C_{10} alkylene-glycol, and

ii) purification of iohexol as prepared in i) comprising using the same C_1-C_5-monoalkylether of a C_3-C_{10} alkylene-glycol as used in i).

2. A method as claimed in claim 1 wherein step ii) is performed after the salt content produced in step i) is reduced.

3. A method as claimed in claimed 1 or 2 wherein said C_1-C_5-monoalkylether of a C_3-C_{10} alkylene-glycol amount in step ii) is adjusted.

4. A method as claimed in claims 1 to 3 wherein said C_1-C_5-monoalkylether of a C_3-C_{10} alkylene-glycol is 1-methoxy-2-propanol.

5. A method as claimed in claims 1 to 4 wherein said C_1-C_5-monoalkylether of a C_3-C_{10} alkylene-glycol in step ii) is mixed with other solvents thus forming a solvent mixture.

6. A method as claimed in claim 5 wherein said other solvents comprise methanol.

7. A method as claimed in claims 5 or 6 wherein the amount of said solvent mixture is adjusted to 2-6 ml 1-methoxy-2-propanol/g iohexol, 0-1 ml methanol/g iohexol and 0.001-0.3 ml water/g iohexol.

8. A method as claimed in claims 5 to 7 wherein isopropanol is added to the solvent mixture.

9. A process for the preparation of iohexol comprising reacting 5-(acetamido)-N,N'-bis(2,3-dihydroxypropyl)-2,4,6,triiodoisophtalamide with a 2,3-dihydroxypropylating agent in the presence of a base and of a solvent comprising a C_1-C_5-monoalkylether of a C_3-C_{10} alkylene-glycol.

10. A process as claimed in claim 9 wherein said solvent is 1-methoxy-2-propanol.

11. A process as claimed in claim 9 or 10 wherein said solvent is mixed with other solvents thus forming a solvent mixture.

12. A process as claimed in claims 9 to 11 wherein said other solvents comprise methanol and/or water.

13. A process as claimed in claim 11 or 12 wherein said solvent mixture comprises 1-methoxy-2-propanol and 0-40 volume % of methanol.

14. A process as claimed in claim 11 or 12 wherein said solvent mixture comprises 1-methoxy-2-propanol and 0-20 volume % of water.

15. A process as claimed in claims 9 to 14 wherein said 2,3-dihydroxypropylating agent is 1-chloro-2,3-propanediol.

Abstract:

The present invention relates to a process for the preparation of iohexol, 5-[N- (2,3-dihydroxypropyl) -acetamido]-N,N'-bis(2,3 -dihydroxypropyl)-2,4,6-triiodoisophtalamide, and to a method of purifying iohexol.

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